A STUDY OF ALPHA GAMMA DIKETONIC ACIDS

A THESIS

Submitted in partial fulfillment of
the requirements for the degree

of

Master of Science in Chemistry

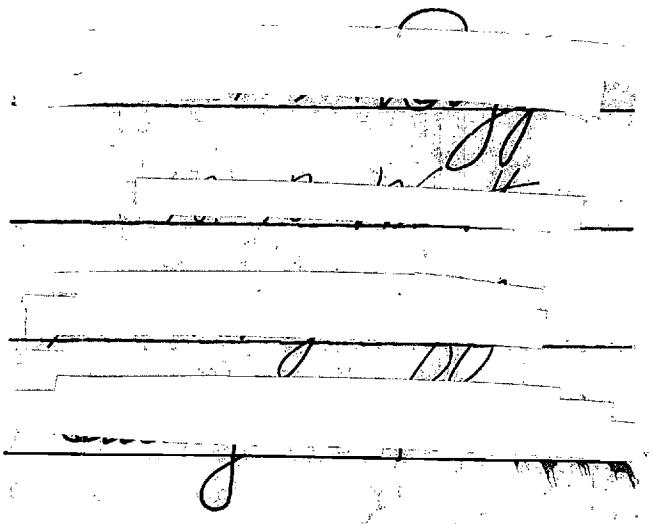
by

Carl Bordenca

Georgia School of Technology
Atlanta, Georgia
1938

4565

APPROVED



ACKNOWLEDGEMENTS

In the completion of this work, I should like to express my sincerest thanks to Dr. W. F. Gresham, not only for his suggestion of the problem, but also for the invaluable aid which he gave so freely. I should like to thank Mr. C. A. Wells of the Department of Chemistry and his students for their analysis of a copper salt. Finally, I am indebted to Dr. B. B. Wroth for his timely suggestions and advice.

C. B.

May 1, 1938

Table of Contents

FOREWORD

A study of the reactions of alpha gamma diketonic acids should afford a means of comparison of their reactions with those of alpha and gamma ketonic acids as well as beta diketones. With this object in view, two types of reactions were considered: acylation and bromination.

The primary purpose of this work has been the study of acylating agents on alpha gamma diketonic acids, most of which were new compounds. The action of acetic anhydride has been studied in particular, with the action of acetyl chloride, benzoyl chloride, and propionic anhydride being considered less extensively.

To a lesser extent there was attempted a study of the effect of bromination. In this instance, however, the difficulty involved in the isolation of the products, as well as the fact that the yields were small, prevented the further investigation of this phase of the problem.

In the case of benzoyl pyruvic acid, there was prepared the copper salt in order that the dibasic nature of this acid might be established further.

Analysis of the various products obtained was made using the semi-micro apparatus described in "Experiments in Organic Chemistry" by L. F. Fieser. A simple modified procedure using ordinary analytical balances was followed. In carrying out the various reactions of the acids and their derivatives, quantities of one gram or less were usually used.

HISTORICAL

The first alpha gamma diketonic acid to be studied in detail was benzoyl pyruvic acid, which was prepared by Bromme and Claisen[1] by the condensation of acetophenone and ethyl oxalate, using sodium ethoxide as the condensing agent.

$$C_6H_5\text{-}CO\text{-}CH_3 + H_5C_2OOC\text{-}COOC_2H_5 = C_6H_5\text{-}CO\text{-}CH_2\text{-}CO\text{-}COOH$$

These authors found that the acid crystallized from ethyl alcohol and water or acetic acid and water with one molecule of water of crystallization. The mono-hydrate yielded the anhydrous compound when heated at 90-100°. Benzoyl pyruvic acid, they found, is a strong acid, forming a mono- and a di-sodium derivative. The di-sodium salt is basic and is decomposed by boiling in water into acetophenone and oxalic acid. The mono-sodium salt is stable under these conditions. When the mono-sodium salt is tested with ferric sulfate, there is formed a dark violet color indicating an enolic modification. By the action of aniline in an alcoholic solution, there is formed the anil of the alpha-carbonyl group.

$$C_6H_5\text{-}CO\text{-}CH_2\text{-}CO\text{-}COOH + C_6H_5\text{-}NH_2 = C_6H_5\text{-}CO\text{-}CH_2\text{-}\overset{\overset{N\text{-}C_6H_5}{\|}}{C}\text{-}COOH$$

However, the work of Bromme and Claisen was concerned more with the study of the ethyl ester than with the acid itself.

E. Erlenmeyer, Jr.[2] later reduced benzoyl pyruvic acid with sodium amalgam using ferric chloride as an indicator. Upon reduction, the acid

[1] Bromme and Claisen, Ber. 21, 1131-46

[2] E. Erlenmeyer, Ber. 45, 3767-9

gave gamma-phenyl alpha-hydroxy butyro-lactone.

$$C_6H_5\text{-}CO\text{-}CH_2\text{-}CO\text{-}COOH + (H) = C_6H_5\text{-}\underset{\displaystyle O\text{——}C=O}{CH}\text{-}CH_2\text{-}CHOH$$

Mumm and Munchmeyer[3] were able to prepare benzoyl pyruvic acid from oxymethylene acetophenone. They formed the sodium salt, the oxime of which upon dehydration and rearrangement gave alpha-phenyl isoxazol.

$$\underset{\text{oxymethylene acetophenone}}{C_6H_5\text{-}CO\text{-}CH{=}CHOH} = C_6H_5\text{-}CO\text{-}CH{=}CHONa = C_6H_5\text{-}\underset{\displaystyle N\text{-}OH}{C}\text{-}CH{=}CHONa = C_6H_5\text{-}\underset{\displaystyle O\text{——}N}{C}{=}CH\text{-}CH$$

By forming alpha-phenyl isoxazol methyl sulfate and treating it with potassium cyanide, there is formed benzoyl pyruvic acid nitrile α-methyl imide. The latter compound upon hydrolysis yielded benzoyl pyruvic acid, the intermediate product of the hydrolysis being the acid amide.

$$\underset{\alpha\text{-phenyl isoxazol}}{C_6H_5\text{-}C{=}CH\text{-}CH} + CH_3HSO_4 = C_6H_5\text{-}\underset{\displaystyle O\text{——}N\text{-}CH_3}{C}{=}CH\text{-}CH \xrightarrow{KCN} C_6H_5\text{-}CO\text{-}CH_2\text{-}\underset{\displaystyle N\text{-}CH_3}{C}\text{-}CN =$$

$$C_6H_5\text{-}CO\text{-}CH_2\text{-}CO\text{-}CONH_2 = \underset{\text{benzoyl pyruvic acid}}{C_6H_5\text{-}CO\text{-}CH_2\text{-}CO\text{-}COOH}$$

The work of Mumm and Munchmeyer was concerned more with the derivatives of the α-methyl imide of benzoyl pyruvic acid than with the acid itself. The starting point in the synthesis of most of the derivatives was α-phenyl isoxazol. All of the products intermediate between benzoyl pyruvic α-methyl imide and benzoyl pyruvic acid were isolated.

Finally, benzoyl pyruvic acid was studied by Salvatori[4] who prepared

[3] Mumm and Munchmeyer, Ber. 43, 3335-43

[4] Salvatori, G., 21 II, 286

the monoxime by heating the acid with hydroxylamine in an excess of sodium carbonate.

$$C_6H_5-CO-CH_2-CO-COOH + NH_2OH = C_6H_5-CO-CH_2-\underset{\underset{N-OH}{\|}}{C}-COOH$$

The second alpha gamma diketonic acid to be studied in some detail was aceto-pyruvic acid. Mumm and Bergell[5] attempted to prepare this acid in a manner analagous to that used by Mumm and Munchmeyer in their synthesis of benzoyl pyruvic acid, namely, by the formation of α-methyl isoxazol and its transformation into the acid. They succeeded, however, in obtaining only the amide of the acid by this method. Using the method of Claisen and Stylos[6] of condensing acetone and ethyl oxalate in the presence of sodium ethoxide, the ethyl ester of the acid was prepared. The sodium salt of the ethyl ester of aceto-pyruvic acid was then hydrolysed with sodium hydroxide and this yielded the acid.

The authors found that aceto-pyruvic acid upon heating decomposed into aceto-acetaldehyde.

$$CH_3-CO-CH_2-CO-COOH = CH_3-CO-CH_2-CHO + CO_2$$

When tested with ferric chloride, it is colored red instantly, and when it is titrated with a strong base using phenolphthalein as the indicator, it gives the indication of being a dibasic acid.

When it is treated with benzaldehyde, it forms the mono-benzal compound.

$$CH_3-CO-CH_2-CO-COOH + C_6H_5-CHO = CH_3-CO-\underset{\underset{CH-C_6H_5}{\|}}{C}-CO-COOH$$

With aniline, there are possible two products depending on the conditions

[5] Mumm and Bergell, Ber. 45, 3040

[6] Claisen and Stylos, Ber. 20, 2188

of the reaction. When in water solution, there is formed the anilide, $CH_3-CO-CH_2-CO-CONHC_6H_5$, while in alcoholic solution there is formed the α-phenyl imide of the acid, $CH_3-CO-CH_2-C(=N-C_6H_5)-COOH$

Finally, aceto-pyruvic acid when treated with aqueous ammonia or alkalies is cleaved, forming acetone and oxalic acid.

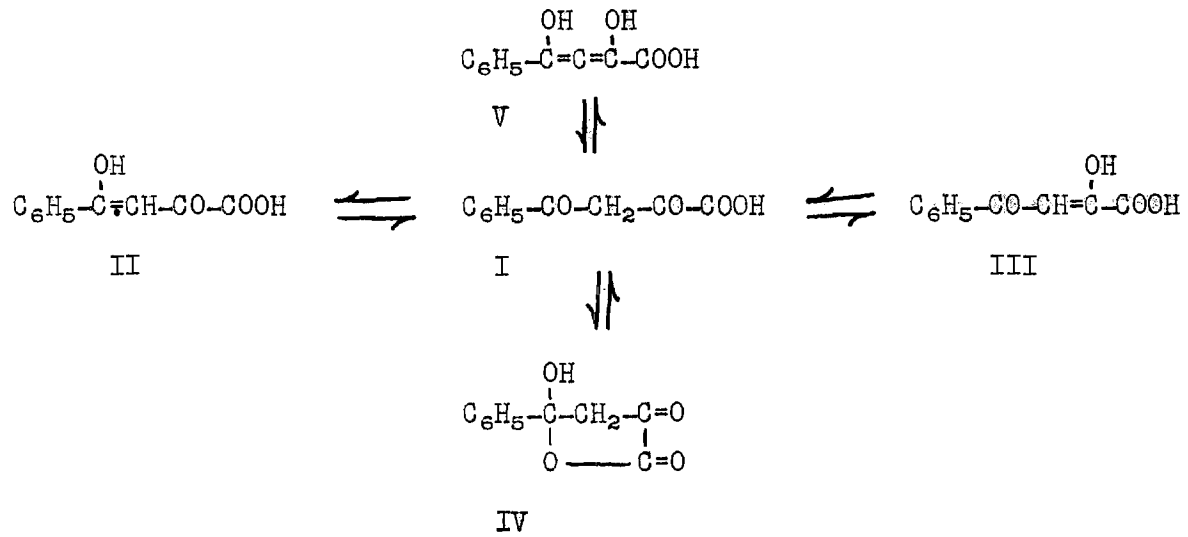
$$CH_3-CO-CH_2-\underset{H}{\underset{|}{C}}(OH)-CO-COOH$$

As in the study of benzoyl pyruvic acid, more emphasis has been placed on the study of the ester than on the acid itself.

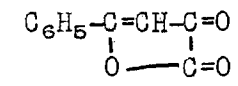
BENZOYL PYRUVIC ACID

I. Reaction with Acetic Anhydride

In the ozonization experiments on the ethyl ester of benzoyl pyruvic acid, which were carried out by Scheiber and Herold[7], there were indications that the ester existed in equilibrium with its mono-enolic forms and probably its dienolic forms. By analogy, it would seem quite reasonable that the acid could exist in equilibrium with its two mono-enolic forms II and III, the lactol IV and its dienolic form V.



By the reaction of acetic anhydride, there could be formed any of the acyl derivatives or possibly a mixture of derivatives. The C-acyl derivative of I might be formed or the acetyl derivative of the lactol IV could lose acetic acid forming an alpha-oxo-croton lactone VI.

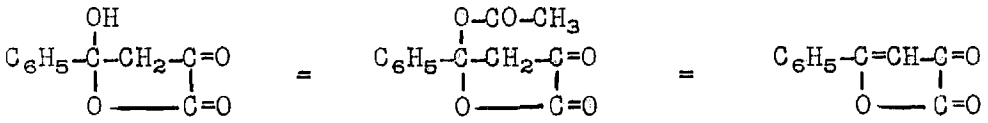


VI

[7] Scheiber and Herold, Ann. 405, 320 (1914)

A suspension of benzoyl pyruvic acid in acetic anhydride was treated with a trace of sulfuric acid. The acid dissolved rapidly giving a yellow solution which immediately precipitated bright yellow crystals. These crystals, when recrystallized from chloroform, melted with decomposition at 124-125°. The formation of yellow crystals in this manner would indicate that the product was not an acetyl derivative because this would be soluble in acetic anhydride. Then, too, none of the possible acetyl derivatives would be colored. The yellow color of the product and its insolubility in acetic anhydride could be accounted for, however, on the assumption that gamma-phenyl alpha-oxo croton lactone (VI) had been formed. This compound has an alpha beta unsaturated ketone structure and an alpha di-ketone structure. Both of these systems impart a color to the compounds in which they appear. All alpha di-ketones are bright yellow in color and alpha beta unsaturated ketones are usually of a light yellow color. A study of the reactions of the yellow compound and a determination of its carbon and hydrogen content established its structure to be that of gamma-phenyl alpha oxo croton lactone (VI).

The oxo-croton lactone was probably formed by way of the O-acetyl derivative of the lactol VII. The lactol acetate loses a molecule of acetic acid spontaneously just as the lactol acetates of certain gamma ketonic acids studied by Kohler, Peterson and Bickel[8].



VII

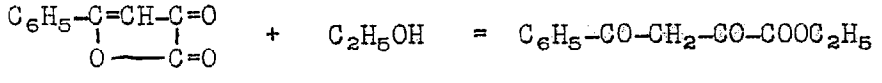
Gamma-phenyl alpha-oxo croton lactone, quite unlike other croton lactones, is easily opened to benzoyl pyruvic acid and some of its derivatives.

[8] Kohler, Peterson and Bickel, J:A.C.S. 56, 2000 (1934)

When the lactone is allowed to stand in the atmosphere of the laboratory for several days, the yellow crystals add water and revert to the parent acid. When the lactone is suspended in water the reaction is much faster. In the latter case, only a few hours are necessary for the complete conversion. When dilute solutions of acids and bases are used, the conversion is even more rapid. Attempts to reduce the lactone using zinc dust and dilute acetic acid brought about the opening of the lactone ring.

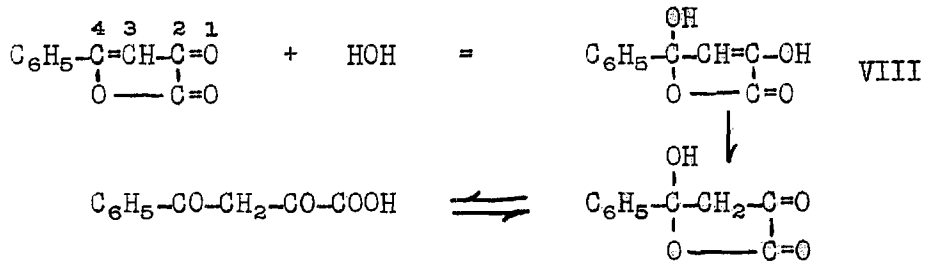
There is apparently no change, when gamma-phenyl alpha-oxo croton lactone is placed out of contact with the atmosphere. A sample of the lactone was kept in a vacuum desiccator for a period of two months, at the end of which time, the color remained the same and when the melting point of the material was taken, there was no difference from the melting point of a freshly prepared sample.

The ease of the opening of the lactone ring is shown in cases other than in the presence of acids, bases and moisture. If the lactone is boiled in alcohol, it dissolves in this solvent quite rapidly. When the excess solvent is evaporated, the ester of benzoyl pyruvic acid remains. When ethyl alcohol was used in this fashion, the ethyl ester was formed. No formal analysis was made of the ester except a melting point determination which corresponded to the melting point of the ethyl ester of benzoyl pyruvic acid obtained by Bromme and Claisen[1].



The opening of the lactone ring of gamma-phenyl alpha-oxo croton lactone may be explained by assuming 1,4-addition of water and alcohol to the alpha-beta unsaturated ketone system. In the case of the water there is formed the enolic modification of the lactol of benzoyl pyruvic acid VIII, which then ketonizes and opens up to the parent acid. A similar addition

might be postulated for the alcohol.



VIII

II. Reaction with Other Acylating Agents and with Bromine

The formation of gamma-phenyl alpha-oxo-croton lactone is not specific to acetic anhydride. When benzoyl pyruvic acid is suspended in propionic anhydride, and the mixture treated with a trace of sulfuric acid, there is formed the lactone in a way similar to that when acetic anhydride is used. The reaction in the case of propionic anhydride is appreciably slower, but the yield is practically quantitative, as it was in the case of the acetic anhydride.

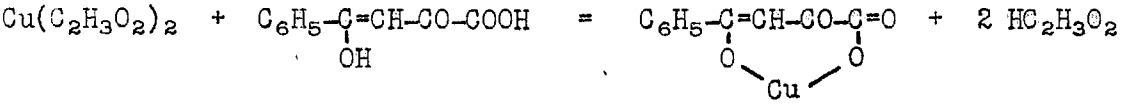
However, when other acylating agents are substituted and the conditions are kept the same, the results were found to be different. Benzoyl chloride was used to suspend the benzoyl pyruvic acid, and when the mixture was treated with sulfuric acid, there was formed a yellow solution, which, when treated with petroleum ether, gave crystals resembling those of the lactone. However, repeated recrystallizations of the material did not change the melting point range, which was large enough to indicate that a mixture had been formed. When acetyl chloride was used, a mixture of substances was apparently formed also, as indicated by the wide melting point range of the product, even after repeated recrystallizations.

Bromination of benzoyl pyruvic acid was attempted first by the addition of bromine to a suspension of the acid in chloroform. The bromine in this case was appently ineffective as the acid was almost completely recovered.

However, when the acid is suspended in acetic acid and treated with bromine, there is a definite effect. When the reaction mixture was allowed to stand for 18 hours, there were formed crystals which after several recrystallizations gave a melting point range of 110 - 120°. Apparently all of the acid had not been brominated.

III. Formation of Its Copper Salt

The dibasic nature of benzoyl pyruvic acid had been shown by the formation of the disodium derivative. From this, there arises the question as to the reaction of the acid with a di-valent metallic ion. Because of the ease of analysis, copper was chosen. Benzoyl pyruvic acid was dissolved in ether and to the solution added a saturated solution of copper acetate and the mixture shaken. Immediately there is formed a green precipitate. Analysis of the compound showed that the ratio of the acid to the copper was 1:1. On this basis, the yield obtained was the theoretical one. The reaction may then be represented:



p-BROMO-BENZOYL PYRUVIC ACID

Its Preparation and Reaction with Acetic Anhydride

The preparation of p-bromo-benzoyl pyruvic acid was carried out using the method which was used by Bromme and Claisen[1] in the preparation of benzoyl pyruvic acid. p-Bromo-acetophenone and ethyl oxalate were added to a solution of sodium in ethyl alcohol with the production of a pasty mass. When the alcohol was evaporated, and the material added to water, a portion was found to be insoluble. The insoluble portion, as was the case in the preparation of benzoyl pyruvic acid, was probably the oxalyl-diacetophenone derivative. The mixture was filtered and the filtrate carefully acidified with acetic acid, whereupon there was precipitated a crystalline substance with a slight yellow color. This solid upon drying was found to be practically insoluble in all ordinary organic solvents. Upon the assumption that the mono-sodium salt* of p-bromo-benzoyl pyruvic acid had been formed, the material was shaken with dilute hydrochloric acid and the mixture extracted with ether. Upon the evaporation of the ether, there remained crystals which were easily soluble in methyl alcohol and when recrystallized from this solvent gave large plate-like crystals with a slight yellow color. When heated at 70° for an hour, the crystals turn dark yellow and when analysed give inconsistent results as a result of probable decomposition. The material may be heated at 50° without appreciable change. Analysis of the recrystallized material corresponded to that of p-bromo-benzoyl pyruvic acid. The acid melts with decomposition at 169°.

$$BrC_6H_4\text{-}CO\text{-}CH_3 + H_5C_2OOC\text{-}COOC_2H_5 = BrC_6H_4\text{-}CO\text{-}CH_2\text{-}CO\text{-}COOH$$

* When a sample of this material is ignited, there remains a white solid which gives a test for both sodium and carbonate ions when dissolved in water.

When the acid is tested with a solution of ferric chloride in methyl alcohol, there is formed the dark violet color indicative of the presence of an enol. When the acid is suspended in acetic anhydride and treated with a trace of sulfuric acid, there is formed a yellow precipitate which when analysed proved to be gamma-(p-bromo-phenyl) alpha-oxo croton lactone. The reactions of this lactone parallel closely those of alpha-oxo gamma-phenyl croton lactone. When gamma-(p-bromo-phenyl) alpha-oxo croton lactone is recrystallized from chloroform, it melts with decomposition at 139 - 140°.

p-METHYL-BENZOYL PYRUVIC ACID

Its Preparation and Reaction with Acetic Anhydride

p-Methyl-benzoyl pyruvic acid was prepared by the condensation of ethyl oxalate and p-methyl-acetophenone, using sodium ethoxide as the condensing agent. p-Methyl-acetophenone and ethyl oxalate were added to the sodium ethoxide solution with the formation of a pasty mass. The excess alcohol was evaporated and the remaining solid was treated with water. Most of the material dissolved, leaving the by-product which is usual in this type of reaction, namely, oxalyl di-(p-methyl-acetophenone). As in the case of the p-bromo compound, there is formed upon the addition of acetic acid to the filtrate after the removal of the by-product the mono-sodium salt of p-methyl-benzoyl pyruvic acid. The acid is formed from the salt by suspending the salt in dilute hydrochloric acid and extracting the mixture with ether. Upon evaporation of the ether, there are formed crystals with a slight yellow color. Recrystallization using methyl alcohol yielded crystals which melted with decomposition at 141 - 142°. Analysis of the recrystallized material corresponded to that of p-methyl-benzoyl pyruvic acid.

$$CH_3-C_6H_4-CO-CH_3 + H_5C_2OOC-COOC_2H_5 = CH_3-C_6H_4-CO-CH_2-CO-COOH$$

When the acid is tested with a methyl alcoholic solution of ferric chloride, there is formed the dark red color which is characteristic of enolic compounds. When the acid is suspended in acetic anhydride and treated with a trace of sulfuric acid, there is formed a yellow precipitate which when analysed proved to be gamma-(p-methyl-phenyl) alpha-oxo croton lactone.

$$CH_3-C_6H_4-CO-CH_2-CO-COOH = CH_3-C_6H_4-\underset{\displaystyle O}{\overset{\displaystyle |}{C}}=CH-\underset{\displaystyle O}{\overset{\displaystyle |}{C}}=O$$
$$\qquad\qquad\qquad

2, 4, 6- TRI-METHYL-BENZOYL PYRUVIC ACID

Its Preparation and Reaction with Acetic Anhydride

The procedure used in the preparation of 2,4,6,-tri-methyl-benzoyl pyruvic acid was slightly different from the procedure used in the preparation of the other acids of this group. Usually upon the addition of the oxalate and ketone mixture to the solution of sodium ethoxide, there is formed a precipitate immediately. When 2,4,6-trimethyl-acetophenone[9] and ethyl oxalate are added to the sodium ethoxide solution, there is formed a viscous, dark brown solution. This solution was evaporated to dryness leaving a dark yellow solid, which was suspended in water. This mixture was filtered and the filtrate carefully acidified with acetic acid. This precipitated the mono-sodium salt just as in the case of the p-bromo- and p-methyl-derivatives. The sodium salt was suspended in a dilute solution of hydrochloric acid and the mixture extracted with ether. Upon evaporation of the ether there remained a pasty mass which seems to consist of some oil along with some solid. The material was carefully extracted with chloroform and recrystallized using a mixture of chloroform and petroleum ether. It was found that this acid is particularly soluble in the ordinary solvents and was soluble to some extent in hot water. A mixture of chloroform and petroleum ether was found to work to the best advantage. The recrystallized acid melted with decomposition at 116 - 117°.

$$(CH_3)_3\text{-}C_6H_2\text{-}CO\text{-}CH_3 \quad + \quad H_5C_2OOC\text{-}COOC_2H_5 \quad = \quad (CH_3)_3\text{-}C_6H_2\text{-}CO\text{-}CH_2\text{-}CO\text{-}COOH$$

When the acid is suspended in acetic anhydride and treated with a trace of sulfuric acid, the acid dissolves completely without further action.

[9] Prepared according to the method described in J.A.C.S. 46, 1889-96

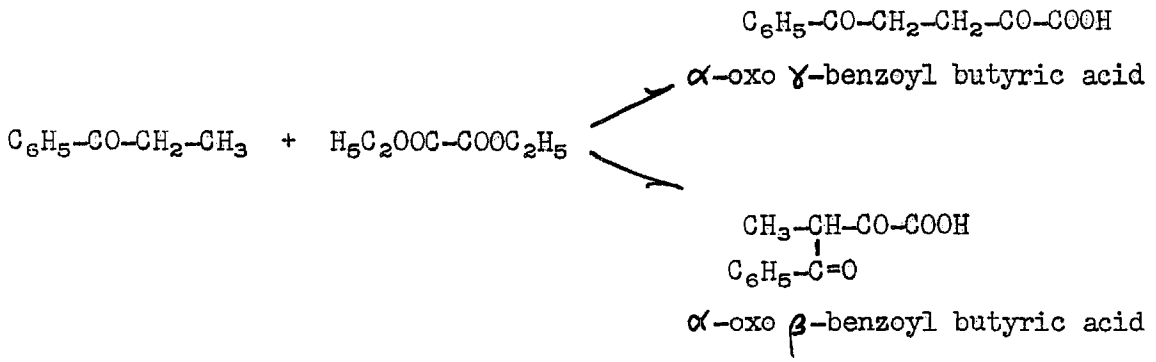
Indications are that the O-acetyl derivative had been formed from the enol and that this compound is stable even in the presence of sulfuric acid. Since there are present two methyl groups in the positions ortho to the carbonyl group, it is quite likely that the prevention of the usual lactone ring formation is due to steric hindrance.

When the acid is treated with a methyl alcoholic solution of ferric chloride, there is formed a dark violet color showing the presence of an enol.

The composition of the trimethyl acid was confirmed by analysis.

ALPHA-OXO-BETA-BENZOYL BUTYRIC ACID AND ACETO-PYRUVIC ACID

An attempt was made to synthesize alpha-oxo-beta-benzoyl butyric acid using the usual method of condensation by the action of sodium ethoxide dissolved in absolute ethyl alcohol on a mixture of propiophenone and ethyl oxalate. To be sure, there would be possible the formation of either the desired acid or the corresponding gamma-benzoyl derivative. Under the conditions of the experiment, however, it was supposed that the beta-benzoyl



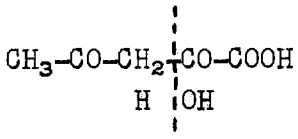
derivative would be formed.

When the mixture of propiophenone and ethyl oxalate was added to the sodium ethoxide solution in absolute alcohol, there was formed a light brown solution. This solution when heated on a water bath turned darker but failed to yield a precipitate on standing. A portion of this solution when diluted with a small amount of water precipitated a solid. When the solid was suspended in dilute hydrochloric acid and extracted with ether, there was complete solution. Upon evaporation of the ether, there remained an oil which hardened to a semi-solid when allowed to stand over-night. Cooling with ice failed to complete the solidification. Use of solvents other than ether was also without avail.

A better method of obtaining the acid would probably have been to evaporate to dryness the original solution of propiophenone and ethyl

oxalate and sodium ethoxide in absolute alcohol. This method was not tried, however.

Attempts to prepare aceto-pyruvic acid using the method of Mumm and Bergell[5] were quite unsuccessful. These authors claim that the acid could be prepared by the hydrolysis of the sodium salt of ethyl aceto-pyruvate[10] using a 4 normal solution of sodium hydroxide and heating at the boiling point for a period of one and one-half hours. In another portion of their paper, these authors also make the statement that aceto-pyruvic acid is cleaved by aqueous ammonia and alkalies to give acetone and oxalic acid in the following manner:



Since very little work has been done on the acid itself, this discrepancy has passed unnoticed. Attempts were made to hydrolyse the sodium salt of the ethyl ester of aceto-pyruvic acid using very dilute solutions of sodium hydroxide but the prolonged heating required by the method of Mumm and Bergell resulted only in the formation of oxalic acid.

Further investigation of this phase of the problem might be of interest and value.

[10] Organic Synthesis, Vol. 6, pp 40-42

EXPERIMENTAL

Preparation of Benzoyl Pyruvic Acid: In the preparation of benzoyl pyruvic acid, the method of Bromme and Claisen[1] was used with the production of the acid in 85 % yields. The anhydrous acid was prepared by dissolving the acid in chloroform and reprecipitating the acid by partial evaporation of the solvent. The acid melted with decomposition at 153 - 154°.

Preparation of Gamma-Phenyl Alpha-Oxo Croton Lactone (VI): To a suspension of 2 grams of benzoyl pyruvic acid in 5 cc. of acetic anhydride there was added one drop of concentrated sulfuric acid. The mixture was stirred. The acid dissolved immediately with the formation of a light yellow solution which rapidly deposited fine yellow crystals. After cooling thoroughly in an ice bath, the needle crystals were separated by filtration and washed with petroleum ether. The yield was 1.8 grams or approximately quantitative. After recrystallization from dried chloroform, the material melted with decomposition at 124 - 125°. The decomposition temperature varies somewhat with the rate of heating.

Calculated for $C_{10}H_6O_3$: C, 68.9; H, 3.4. Found: C, 68.3; H, 3.1.

Action of Aqueous Sodium Bicarbonate on (VI): To an aqueous solution of sodium bicarbonate was added with shaking 1 gram of the oxo-croton lactone. Upon shaking, the lactone dissolved slowly yielding a reddish violet solution. Careful addition of dilute hydrochloric acid gave a precipitation of slightly yellow crystals. These were dissolved in chloroform and the solution evaporated to a small volume. Upon standing, the solution gave stout crystals melting with decomposition at 153°. A mixed melting point with an authentic sample of benzoyl pyruvic acid gave no depression of the melting point.

Action of Sodium Methylate on (VI): To a solution of 0.1 gram of sodium in methyl alcohol was added 1 gram of the oxo-croton lactone. Dissolution was rapid yielding a reddish violet solution. The solution when treated in the usual fashion deposited crystals of benzoyl pyruvic acid.

Action of Zinc Dust and Acetic Acid on (VI): A suspension of 1 gram of the lactone in glacial acetic acid was treated gradually with 2 grams of zinc dust. After removing the excess zinc, the solution was poured into water which yielded benzoyl pyruvic acid.

Action of Ethyl Alcohol on (VI): 0.5 gram of the lactone was suspended in 5 cc. of ethyl alcohol and the mixture heated. The lactone dissolved giving a dark yellow solution which on continued heating became light yellow. Upon the evaporation of the solvent there remained a solid, which when recrystallized from petroleum ether gave a melting point of 43°, which is the melting point given by Bromme and Claisen for the ethyl ester of benzoyl pyruvic acid.

Reaction of Propionic Anhydride on Benzoyl Pyruvic Acid: To a suspension of 2 grams of benzoyl pyruvic acid in 5 cc. of propionic anhydride was added one drop of concentrated sulfuric acid. The mixture was stirred. The acid dissolved slowly with the formation of a light yellow solution which then deposited yellow crystals. After cooling the mixture, it was filtered and the crystals recrystallized from chloroform. The melting point was the same as that obtained for the oxo-croton lactone and a mixed melting point of the two gave no depression.

Reaction of Benzoyl Pyruvic Acid and Benzoyl Chloride: 1 gram of benzoyl pyruvic acid was suspended in 15 cc. of benzoyl chloride. The mixture was carefully stirred and one drop of concentrated sulfuric acid added. The materials dissolved completely yielding a yellow solution. To this was

added 5 cc. of benzene and then petroleum ether to effect precipitation. 0.6 gram of a yellow crystalline material was precipitated and recrystallization from chloroform was made twice. The melting point was not sharp after this treatment.

Action of Acetyl Chloride on Benzoyl Pyruvic Acid: One gram of benzoyl pyruvic acid was suspended in 15 cc. of acetyl chloride. To this mixture was added a drop of concentrated sulfuric acid. The mixture turned yellow and solution was complete after stirring for a few minutes. Excess acetyl chloride was removed by suction, precipitating a yellow solid. This material was filtered and recrystallized twice from chloroform. The melting point indicated the material to be a mixture.

Bromination of Benzoyl Pyruvic Acid: 1 gram of benzoyl pyruvic acid was suspended in 10 cc. of chloroform and cooled to 5°. To this mixture was added dropwise 0.28 cc. of bromine. The mixture was shaken until complete solution was effected. The solvent was evaporated by suction leaving a yellow oil. This oil was taken up in chloroform and the solution allowed to stand two days. The solvent was evaporated by suction and the solution filtered. White crystals were obtained having a melting point of 154°. The original acid had been recovered.

Bromination of Benzoyl Pyruvic Acid: 5 grams of benzoyl pyruvic acid were suspended in 30 cc. of glacial acetic acid. The mixture was placed in a shallow dish and 1.8 cc. of bromine added with stirring. The solution was allowed to be evaporated by standing. The mixture was filtered and the filtrate extracted with petroleum ether. The precipitate was easily soluble in chloroform and after repeated recrystallization gave a melting point range of 110 - 120°. Evaporation of the petroleum ether extract gave an oil.

Copper Derivative of Benzoyl Pyruvic Acid: 1 gram of the acid was dissolved in ether and placed in a small flask. 25 cc. of a saturated solution

of copper acetate were added and the mixture shaken well. A green precipitate was formed which was filtered and washed with water, alcohol and ether and dried. The yield was theoretical: 1.3 grams.

Calculated for the dibasic salt: Cu, 24.9. Found: Cu, 23.5

Preparation of p-Bromo-Benzoyl Pyruvic Acid: 2 moles of sodium were dissolved in absolute alcohol. This solution was heated on a water bath and to this was added a mixture of one mole of ethyl oxalate and one mole of p-bromo-acetophenone dissolved in a minimum of absolute ethyl alcohol. This mixture was heated on a water bath for one half hour. There was formed a semi-solid mass which was freed from excess alcohol and was suspended in water. The mixture was filtered and the filtrate carefully acidified with acetic acid with the precipitation of a slightly yellow solid. This was filtered and suspended in a 0.05 N solution of hydrochloric acid. The solution was extracted twice with ether and the ether evaporated carefully with the deposit of fine crystals. When recrystallized from methyl alcohol, there are formed plate-like crystals melting with decomposition at 169°. The decomposition temperature changes somewhat with the change in the rate of heating. A 50 % yield of the acid was obtained on one run.

Calculated for $C_{10}H_7O_4Br$: C, 44.3; H, 2.6. Found: C, 44.1; H, 2.0

Preparation of Gamma-(p-Bromo-Phenyl) Alpha-Oxo- Croton Lactone: To a suspension of 1 gram of p-bromo-benzoyl pyruvic acid in 5 cc. of acetic anhydride was added one drop of concentrated sulfuric acid. The mixture was stirred and cooled thoroughly in an ice bath. Upon filtering there were separated bright yellow needle crystals which upon recrystallization from chloroform melted with decomposition at 139 - 140°. This lactone was readily soluble in dilute sodium bicarbonate solution which upon acidification reformed the original acid.

Calculated for $C_{10}H_5O_3Br$: C, 47.5; H, 2.0. Found: C, 47.5; H, 2.2

Preparation of p-Methyl-Benzoyl Pyruvic Acid: 2 moles of sodium were dissolved in absolute alcohol. The solution was heated on a water bath and to this added a mixture of one mole of ethyl oxalate and one mole of p-methyl acetophenone. The mixture was heated on a water bath for one-half hour. There was formed a semi-solid mass which was freed from excess alcohol and treated in a manner analagous to that used in the preparation of the p-bromo-derivative described above. The acid was recrystallized from methyl alcohol yielding crystals which melted with decomposition at 141 - 142°. A 60 % yield of the acid was obtained on one run.

Calculated for $C_{11}H_{10}O_4$: C, 64.0; H, 4.9. Found: C, 63.4; H, 4.2.

Preparation of Gamma-(p-Methyl-Phenyl) Alpha-Oxo Croton Lactone: To a suspension of 1 gram of p-methyl-benzoyl pyruvic acid in 5 cc. of acetic anhydride was added a drop of concentrated sulfuric acid. The mixture was stirred and cooled thoroughly in an ice bath. Upon filtering, there were separated bright yellow crystals which upon recrystallization from chloroform gave a melting point with decomposition of 127 - 128°. This lactone was also soluble in a dilute sodium bicarbonate solution which upon acidification reformed the original acid.

Calculated for $C_{11}H_8O_3$: C, 70.2; H, 4.3. Found: C, 69.8; H, 4.0.

Preparation of 2,4,6-Tri-Methyl-Benzoyl Pyruvic Acid: 2 moles of sodium were dissolved in absolute alcohol and the solution heated on a water bath. A mixture of one mole of 2,4,6-trimethyl-acetophenone and one mole of ethyl oxalate were added and the mixture heated on a water bath for one-half hour. There was formed a viscous, brown solution which was placed in an evaporating dish and evaporated to dryness on a water bath. There remained a yellow solid which was ground to a fine powder. This material was suspended in water and the mixture filtered. The filtrate was acidified carefully with acetic acid and allowed to stand overnight. Upon filtering,

there remained a slightly yellow solid which was suspended in a dilute solution of hydrochloric acid and the mixture extracted with ether. Upon the evaporation of the ethereal solution, there remained a pasty mass consisting of some oil. By allowing to stand on a porous plate and by careful extraction with chloroform the oil was removed. The acid was recrystallized from a chloroform and petroleum ether mixture yielding needle crystals which melted with decomposition at 116 - 117°. A 70 % yield was obtained.

Calculated for $C_{13}H_{14}O_4$: C, 66.4; H, 6.0. Found: C, 66.0; 6.0.

Reaction of 2,4,6-Tri-Methyl-Benzoyl Pyruvic Acid with Acetic Anhydride: Upon the addition of 1 gram of the acid to 5 cc. of acetic anhydride, solution took place immediately. One drop of concentrated sulfuric acid was added and when the solution was stirred, it turned very dark as if there were decomposition. The process was repeated and instead of adding a drop of concentrated sulfuric acid, there was added a drop of a solution made by dissolving 0.10 cc. of con. sulfuric acid in 15 cc. of acetic anhydride. The solution turned slightly yellow but no precipitation occurred. Evaporation of the solution to a small volume and cooling with ice were ineffective. Addition of petroleum ether to the solution resulted in the precipitation of an oil.

Alpha-Oxo-Beta-Benzoyl Butyric Acid: 2 moles of sodium were dissolved in absolute alcohol. The solution was heated on a water bath and to it was added a mixture of one mole of propiophenone and one mole of ethyl oxalate. The mixture was heated on a water bath for one-half hour. A portion of the solution was diluted with a small amount of water. There was formed a light yellow precipitate which was filtered. The solid was suspended in a dilute solution of hydrochloric acid and the mixture extracted with ether. The ether was evaporated leaving an oil which was dissolved in chloroform. Upon slow evaporation of the chloroform, the oil remained. When the oil was allowed to stand overnight, there was formed a semi-solid mass which was easily soluble in ether, chloroform, methyl alcohol or acetone. By slow e-

vaporation of a solution of the oil in any of these solvents, the oil was obtained again.

SUMMARY

By the action of acetic anhydride, with a trace of concentrated sulfuric acid, benzoyl pyruvic acid is converted into gamma-phenyl alpha-oxo croton lactone. This is a new type of croton lactone.

Gamma-phenyl alpha-oxo croton lactone is also formed from benzoyl pyruvic acid by the action of propionic anhydride when a trace of concentrated sulfuric acid is added.

Benzoyl pyruvic acid, in solution, must exist in equilibrium with at least a small amount of its lactol.

Gamma-phenyl alpha-oxo croton lactone, unlike other croton lactones, is easily opened to the parent acid by water and dilute solutions of acids and bases. It is opened to the ester by alcohols.

p-Bromo-benzoyl pyruvic acid was prepared by condensing p-bromo-acetophenone and ethyl oxalate using sodium ethoxide as the condensing agent.

p-Bromo-benzoyl pyruvic acid, when suspended in acetic anhydride and treated with a trace of concentrated sulfuric acid, forms gamma-(p-bromophenyl) alpha-oxo croton lactone. The reactions of this lactone parallel those of the gamma-phenyl derivative.

p-Methyl-benzoyl pyruvic acid was prepared by condensing p-methyl-acetophenone and ethyl oxalate using sodium ethoxide as the condensing agent.

p-Methyl-benzoyl pyruvic acid, when suspended in acetic anhydride and treated with a trace of concentrated sulfuric acid forms gamma-(p-methyl-phenyl) alpha-oxo croton lactone.

2,4,6-Trimethyl-benzoyl pyruvic acid was prepared by condensing 2,4,6-trimethyl-acetophenone and ethyl oxalate using sodium ethoxide as the condensing agent. This acid failed to form the lactone in the usual manner. Steric hindrance is postulated.

The copper salt of benzoyl pyruvic acid was prepared and its composition determined.

Attempts to prepare alpha-oxo beta-benzoyl butyric acid and acetopyruvic acid were unsuccessful.

Attempts to brominate benzoyl pyruvic acid were rather unsuccessful.